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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/701,626	RALEIGH ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-10,12-14 and 17-20* is/are pending in the application.

4a) Of the above claim(s) *17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-10,12-14 and 18-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is written in response applicant's papers filed 6/24/05. Following the entry of the papers, claims 1, 5-10, 12-14, and 17-20 are pending. Claims 1 and 7 were amended, and claim 17 is withdrawn from prosecution. This action is **FINAL**.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1, 6, 18, 19, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite for the recitation "flanking repeat sequences" because it is not clear from the claim what the repeat sequences are flanking. The claim appears to imply that the primers hybridize to sequences which flank repeats, however the specification appears to indicate that the primers hybridize to repeats themselves. Clarification is requested. Further, the claim is indefinite because the preamble recites a method for cloning at least one of a restriction endonuclease or a methyl transferase, but the process steps of the claim never positively recite such an outcome, reciting only that the practice of the method include determining whether the encoded polypeptide is a restriction endonuclease or methyl transferase. Thus, it is not clear if the claim is intended to encompass only methods wherein a methyl transferase or restriction endonuclease is cloned or if the claim is also intended to include claims wherein other potential coding sequences are cloned. Claims 5 and 6 are also indefinite over these issues because they depend directly or indirectly from claim 1.

Claims 18, 19, and 20 are indefinite because these claims depend from canceled claim 2. Thus, the limitations of the claims are entirely unclear. Further, if applicant intends for these claims to have depended from claims 1, 5, or 6, the claims are still unclear since these claims are limited to the cloning of a restriction endonuclease and/or a methyl transferase but claims 18, 19, and 20 refer to adhesions, signaling peptides, and detoxifying enzymes. Applicant's intentions regarding these claims are entirely unclear, and thus, these claims could not be further treated on the merits.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1 and 5-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for cloning genes as recited in claim 1 which utilize primers that are fragments of instant SEQ ID NO: 5-SEQ ID NO: 78 for amplification of P. alcaligenes DNA, does not reasonably provide enablement for methods which use any additional oligonucleotide primers to identified flanking repeat sequences. Furthermore, while the specification is enabling for a screening method which isolated gene cassettes, the specification is not enabling for claims which recite the particular genes to be cloned.

Further, claims 7-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of detection of gene cassette arrays in Pseudomonas which utilize instant SEQ ID NO: 5- SEQ ID NO: 91 as primers or probes, or fragments of these sequences (as exemplified in claim 10) as primers or probes, the specification

is not enabling for the use of any or all fragments that would hybridize under any conditions to these sequences. Furthermore, the specification is not enabling for the detection of gene cassette arrays in all Pseudomonas species or in any other genus of prokaryote.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the Invention

The claims 1 and 5-6 are drawn to methods for cloning at least one of a restriction endonuclease or a methyl transferase and include steps of hybridizing oligonucleotide primers to flanking repeat sequences in a cassette array, wherein the primers "have" sequences "contained in" at least one of SEQ ID NO: 5 through SEQ ID NO: 91, amplifying the DNA between the primers and ligating the fragments of step (b) into a vector for cloning the one or more genes. Thus, the nature of the invention is concerned with the isolation of coding sequences from within gene cassettes via amplification using primers that minimally comprise fragments of SEQ ID NO: 5 through SEQ ID NO: 91.

Claims 7-14 recite a method for identifying the presence of a gene cassette array from within a prokaryotic target DNA preparation said method comprising the steps of hybridizing at least one oligonucleotide which is "capable" of hybridizing under "stringent conditions" to one or more DNA sequences selected from SEQ ID NO: 5 through SEQ ID NO: 91 to a DNA preparation and detecting the presence of a stable DNA-DNA hybrid so as to identify a of the presence of a gene cassette array. Nonetheless, the nature of the invention for these claims

requires a relationship between the hybridization oligonucleotide and the presence of a gene cassette array.

Scope of the invention

Claim 1 is broadly drawn to encompass the isolation of any restriction endonuclease or methyl transferase from any organism via amplification with primers to flanking repeat sequences. The claim encompasses the isolation of enzymes, for example from any species of prokaryote, but also from any other organism, including, for example from humans. The primers to be used in the method are minimally defined, with the claim reciting that the primers "have" (which is interpreted as identical to "comprise") sequences that are contained in one of SEQ ID NO: 5 through SEQ ID NO: 91. This language is extremely broad, requiring only that the primers used in the claimed invention have only short fragments of the recited sequence identifiers, since the primers must only include portions "contained in" the sequences. The preamble of the claim defines the cassette array as "being characterized by a plurality of genes where each gene is embedded in a predictable nucleotide sequence including a repeat DNA sequence."

The specification discusses in particular integrons and superintergrons as mobile gene cassettes interspersed in prokaryote genomes. These structures have open reading frames which are separated by gene sequences which are classically referred to as 59-base pair elements in the prior art (see for example Mazel et al., p. 605, 3rd column). A preferred embodiment contemplated by applicants is an embodiment wherein the primers used in claim 1 hybridize within these elements and amplify the intervening sequence, which is expected to contain an open reading frame. The instant specification provides a large number of such sequences for

only a single prokaryotic species, *Psuedomonas alcaligenes*, of which SEQ ID NO: 5 through 91 are representative. No gene cassette arrays or predictable repeat sequences are disclosed in the specification for any other species of *Psuedomonas* or for any other genus or prokaryote.

The claims specifically recite that the claimed method include determining whether the cloned DNA fragments encode a restriction endonuclease or a methyl transferase, and the preamble of the claim goes further so as to recite that the method is "for cloning at least one of a restriction endonuclease or a methyl transferase." However, there is no guidance or direction in the specification as to how to direct isolation so as to specifically obtain either one of these, as required by the claims. Even for *P. alcaligenes*, what type of gene is isolated by the instant method is entirely due to chance since it is entirely unpredictable as to what sequences will be located in the cassette structures. The specification does not provide any guidance as to how to particularly isolate any of the specifically recited gene types. The specification demonstrates that in *P. alcaligenes* a gene encoding the restriction enzyme PacI is embedded in a gene cassette, but the specification does not give any guidance as to the structure of the gene sequence or how it in particular may be cloned. Guidance is given in the specification as to how to screen for a number of different protein activities, but there is no way to predict a priori for Pseudomonas species or for any prokaryote species what type of genes will be isolated using the claimed methods.

The scope of claims 7-14 is also quite broad in nature, owing to the fact that the method claim very broadly defines the oligonucleotide probe used in the assay as being one which "hybridizes to one or more of SEQ ID NO: 5 through SEQ ID NO: 78," and that the claims encompass the detection of gene cassette arrays in any species of prokaryote. Thus, the claim

includes the use of any nucleic acid that hybridizes under any conditions to form a stable hybrid with any portion of any one of these sequences. Though the preamble of the claim recites "A method for identifying the presence of gene cassette arrays," there is no language in the body of the claim to even require that the oligonucleotide probe be specifically indicative of the presence of such arrays. Further, the specification does not specifically or clearly define what is meant by a "gene cassette array" and thus this language can be construed to mean the detection of any nucleic acid construct comprising a gene attached to any other gene, for example. The claim is not limited, for example, to detecting the presence of integron or integron-like structures.

Guidance provided in the specification

The specification hypothesizes that gene cassette arrays (of the integron type) may cluster genes related to pathogenicity and other biochemical functions. The specification provides general guidance as to the amplification and detection of cassette sequences, the cloning of genes, and the screening of genes for biological functions. The specification provides the nucleotide sequence of 73 sequences that were identified as Psuedomonas alcaligenes repeat (PAR) sequences that appear to be similar in structure to the 59-base pair elements present in integrons in other species (E. coli, for example). The specification does not, however, provide any guidance as to the structure (i.e. nucleotide sequence) of additional repeat sequences from any other prokaryote species. The specification suggests that a large number of such sequences is necessary to enable the design of family specific primers (p. 16, first 3rd), and specification further teaches that individual members of the repeated array display imperfect dyad symmetry, making it very likely that PCR primer design will be complicated by hairpin formation or primer dimmers that will hinder amplification (p. 16, 2nd paragraph). The specification does not provide

any guidance, however, as to how to overcome these obstacles for any or all species of prokaryotes, other than the single species for which the practice of the claimed invention is exemplified.

Further, with regard to all of the claims, the specification does not provide any guidance as to which portions of SEQ ID NO: 5 through SEQ ID NO: 91 are necessary for hybridization in order to in fact know that the formation of a specific hybrid or amplification product is in fact indicative of a particular cassette array. This guidance is crucial given the breadth of the claims which include the use of any number of oligonucleotide probes that hybridize to only portions of the disclosed sequences. Absent any further guidance, it is highly unpredictable as to what sequences can be used to detect the gene cassette arrays in prokaryotes other than Pseudomonas alcaligenes.

State of the Prior Art

Applicant summarizes the state of the prior art in the specification when applicant teaches "it has been considered unlikely that these repeat sequences would enable acquisition of cassette-encoded genes by PCR because of the degeneracy of the sequences and the secondary structure encoded by them...(specification, p. 5, lines 29-32)." Even in light of this, however, Mazel et al. (as cited in the prior art rejections herein) do exemplify amplification of cassettes using primers to the repeat regions in V. cholerae. However, at the time the invention was made, extensive sequence information concerning the repeats for other prokaryote species was not known. The absence of this information from the prior art is critical given the importance of this information for designing primers and probes for the practice of the claimed inventions, especially for use in organisms other than the exemplified species..

Working Examples

Turning to the working examples in the specification, Example 1 (beginning on p. 32) discloses the isolation of the genes encoding the restriction enzymes PacI and PmeI from *Psuedomonas alcaligenes* and *P. mendocina*, respectively, using previously taught cloning methods (p. 32, lines 17-22). After cloning of the genes, the surrounding sequence was cloned from both species (p. 32, lines 30-33). Repetitive sequences common to both segments were identified by visual inspection (p. 33, lines 4-5). Additional sequence was isolated from *P. alcaligenes* and was sequenced (p. 33-34). These sequences are given in SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4. Following sequencing a computer search of the 59.4 kilobases of sequence was conducted for putative repeat regions. A set of elements identified by motif searching are given in SEQ ID NO: 5-SEQ ID NO: 78 (p. 36).

Following identification of the elements by motif searching, a Southern blot was carried out against chromosomal DNA of *P. alcaligenes* using hybridization probes SEQ ID NO: 80-83 (p. 37), and multiple fragments in each digest hybridized with the probes (see Figure 8), and applicant teaches that this hybridization indicates that the oligonucleotides represents a repeated sequence (p. 37, last sentence).

The specification provides discussion of a method for detecting cassette arrays in a population by using primers annealing to each end of the repeats separating the cassettes in a PCR experiment, and validate this method using SEQ ID NO: 84 and 85 in six species of *Pseudomonas* (p. 39). Of the six different *Pseudomonas* species tested, two yielded multiple amplification products. Four of the species, therefore, did not yield products.

In example 2, applicants teach PCR amplification of *P. alcaligenes* DNA using primers SEQ ID NO: 86-91 and cloning of the cassettes contained therein (p. 46-47). Applicants further discusses methods of screening the cloned sequences for functional report and assessing clone identity, but these discussions are prophetic in nature (p. 47-51). Thus, the putative genes sequences within the PCR products were not detected. Further, applicants suggest that the cassettes "will encode many different sorts of genes (p. 43, line7)," but do not provide any examples of genes within the putative cassette arrays, other than the genes encoding the restriction enzymes PacI and PmeI.

Thus, the specification does not provide a single working example wherein the claimed method is actually practiced for any species other than *P. alcaligenes*. Further, though the amplification and cloning taught in example 2 is similar to that recited in claim 1, there is no subsequent analysis to determine if in fact the cloned nucleic acids are "genes," which encode any known or unknown polypeptide, particularly any restriction endonuclease or methyltransferase.

Level of Unpredictability

The level of unpredictability with regard to practicing the claimed invention commensurate in scope with the claims is quite high.

For example, it is highly unpredictable as to which sequences can be used to amplify genes contained between repeat regions in cassette arrays for organisms other than Psuedomonas alcaligenes. This unpredictability is highlighted by the fact that primers designed based on the sequences disclosed herein were able to produce amplification products in only two of six different Pseudomonas species tested (see p. 39). Indeed, this problem is further illustrated in the

post-filing date art where Vaisvila et al. (Molecular Microbiology, 2001, 42(3)587-601) attempted to use primers based on *P. alcaligenes* repeats to amplify potential repeated regions in forty-seven different bacterial strains, and positive isolates belonged only to the genus Pseudomonas (p. 594), and of these, products were only amplified from three different species (see figure description 9b). Barker et al. (1994, Journal of Bacteriology, Vol. 176, No. 17) also demonstrate the highly specific nature of the sequence of the repeat elements in VCR, as they teach that a VCR specific probe hybridizes only to some V. cholerae species but no to other Vibrio species or to Aeromonas species tested (p. 5455).

Additional putative primer sequences that might be useful for amplifying different species of prokaryotes would have to be empirically determined, as these sequences are entirely unpredictable. The specification further discusses the unpredictability and difficulty involved in the design of such primers. The specification teaches that these repeat sequences is that the members of a repeated array are degenerate, so that PCR primers hybridizing to most or all of the members are difficult to design, and that accordingly, a large number of such sequences is necessary to enable the design of family specific primers (p. 16, first 3rd). The specification further teaches that individual members of the repeated array display imperfect dyad symmetry, making it very likely that PCR primer design will be complicated by hairpin formation or primer dimmers that will hinder amplification (p. 16, 2nd paragraph). Each of these obstacles would have to be considered empirically for any given species of prokaryote, and so it would be necessary for any species of prokaryote to undertake extensive and unpredictable experimentation in order to obtain the sequence information necessary to practice the claimed invention.

Furthermore, with regard to claim 1, 5, and 6 which all require the isolation of particular types of genes (i.e. those encoding methyl transferases or restriction endonucleases), it would be highly unpredictable as to how to direct the amplification specifically to lead to the cloning of any of these genes, as it is unknown which of these genes are actually present within the cassette arrays in any or all prokaryote species or in other non-prokaryotic species as encompassed by the claims. Barker et al. teach that eight sequenced ORFs from within V. cholerae gene cassettes had no significant similarity to known protein sequences (p. 5456, 1st column). The instant specification provides only speculation that additional examples of these types genes may be identified within the cassette sequences. The claims require that they are located between repeat sequences, as the claims require the cloning of these types of genes. There is not a nexus between the showing in the specification and the instant claims.

With regard to the primers for use in the methods of claims 1, 5, and 6, the selection of primers from those sequences "contained in at least one of" the sequences recited is highly unpredictable due to the broad scope of this recitation and the fact that the claims encompass cloning genes from any species of organism via hybridization to "gene cassette arrays." The specification does not provide any guidance as to which portions of SEQ ID NO: 5 through SEQ ID NO: 91 are critical for the identification of gene cassette arrays, and the claims encompass the use of any nucleic acid that hybridizes under any possible conditions to the disclosed sequences.

Likewise, with regard to claims 7-14, the practice of the instant invention for the "identification of gene cassette arrays" is highly unpredictable due to the broad scope of the hybridization probes recited for use within claim 7 and the fact that the claims encompass detecting "gene cassette arrays" in any species of prokaryote using sequences that hybridize to

portions of SEQ ID NO: 5 through SEQ ID NO: 91. The specification does not provide any guidance as to which portions of SEQ ID NO: 5 through SEQ ID NO: 91 are critical for the identification of gene cassette arrays, and the claims encompass the use of any nucleic acid that hybridizes under any possible conditions to the disclosed sequences.

Conclusion

Thus, in view of this analysis, namely in view of the broad scope of the claims, and the lack of commensurate examples or guidance, in view of the state of the prior art which does not fill the holes lacking in the disclosure, in view of the high level of unpredictability in this technology, as demonstrated and discussed in applicant's specification, it is concluded that it would require undue experimentation to practice the claimed invention commensurate in scope with the instantly pending claims.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 5, and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Aksoy et al. (The Journal of Biological Chemistry, Vol. 269, Issue 20, 14835-14840, 1994).

Askoy et al. teach a method for cloning a methyl transferase comprising the steps of:

(a) hybridizing oligonucleotide primers to identified flanking repeat sequences in the cassette array (p. 14836, 2nd column); and

(b) amplifying the DNA between the hybridized primers of step (a) to produce DNA fragments which contain one or more genes (p. 14836, 2nd column),

(c) ligating the DNA fragments into a vector for cloning (p. 14836, 2nd column), and

(d) determining whether the cloned DNA fragments encode a methyltransferase (p. 14835 and p. 14838, 1st column).

Regarding the limitation in step (a) which recites the use of "primers having sequences contained in at least one of SEQ ID NO: 5 through SEQ ID NO: 91" this recitation is extremely broad with regard to the actual structural limitation put on the primer. The use of "having" is equivalent to "comprising," and thus means that the primers must comprise "sequence contained in" at least one of SEQ ID NO: 5 through 91, but can have any number of additional nucleotides on either end of the primers. The length of the "sequence contained in" is entirely undefined, and thus is inclusive of as few as one or two nucleotides. Thus, the primers taught by Askoy et al. share at least one or two nucleotides with the sequences recited in the claim.

Further regarding the limitation that the cassette array "is a plurality of genes such that each gene is embedded in a predictable nucleotide sequence context including a repeat DNA sequence," this limitation is very broad. Every gene by its very nature is embedded in a nucleotide sequence that is predictable such that it contains repeat sequences within the human genome. That is, to some degree, every sequence in the human genome is flanked by repeat sequences of some length (the claim does not further describe "repeat sequence" so it is inclusive of as few as two repeated nucleotides), and it is reasonable to predict that these are throughout the genome. The primers used by Maskoy et al. were based on amino acid sequences that are repeated in each copy of the genome, and these surround the amplified portion.

With regard to claim 5, the primer contains an EcoRI site for cloning, and with regard to claim 6 the fragments are ligated in order to enable expression.

8. Claims 7, 8, 11, 12, 13, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Barker et al. (Journal of Bacteriology, Sept 1994; as cited in IDS).

Barker et al. teach a method for identifying the presence of gene cassette arrays from within a prokaryotic target DNA preparation comprising the steps of:

(a) hybridizing at least one oligonucleotide to a prokaryotic DNA preparation, wherein at least one oligonucleotide is capable of hybridizing under stringent conditions to one or more DNA sequences selected from SEQ ID NO: 5 through SEQ ID NO: 91 to a DNA preparation; and

(b) detecting the presence of a stable DNA-DNA hybrid.

Namely, Barker et al. teach southern hybridization of a VCR-specific probe to V. cholerae samples (p. 5454; Figure 4). This probe is considered to be an oligonucleotide which is "capable of hybridizing under stringent conditions" to "one or more of SEQ ID NO: 5 through SEQ ID NO: 91" because the claim does not set forth any hybridization conditions or requirements, nor does the claim require that the probe hybridize to the full length of any of the specific sequences. Probe used by Barker et al. is "capable" of hybridizing to SEQ ID NO: 5 through SEQ ID NO: 91 under stringent conditions, albeit conditions of "low" stringency. The use of the word "stringent" in the claim does not provide a limitation of the degree of stringency, only that the conditions are some degree of stringency. Barker et al. test individual strains of V.

cholarae (see figure 7 description), and test a group of strains, albeit each individually. The samples are considered "environmental samples" because this organism is present in the environment at least of the cell cultures.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 5, and 6 rejected under 35 U.S.C. 103(a) as being unpatentable over Mazel et al. (Science, Vol. 280, April 1998) in view of Ogawa et al. (Micorbiol. Immunol., Vol. 37, No. 8, p. 607-616).

Mazel et al. teach a method of cloning one or more prokaryotic genes in a cassette array, the array being characterized by a plurality of genes where each gene is embedded in a predictable nucleotide sequence including a repeat DNA sequence, the method comprising the steps of:

(a) hybridizing oligonucleotide primers to identified flanking repeat sequences in the cassette array; and

(b) amplifying the DNA between the hybridized primers of step (a) to produce DNA fragments which contain one or more genes.

Specifically, turning to p. 607, Mazel et al. teach that Vibrio isolates were screened by means of oligonucleotide primers corresponding to the most conserved regions of the VCR

sequences. The "VCR" sequences are DNA repeat sequences within the Vibrio cholerae genome. Mazel et al. teach that VCR cassettes were identified in 6 of the 7 isolates tested (see Table 2). Mazel et al. further teach that some of these cassettes were sequenced from V. metschnikovii PCR products (2nd column), including one that contained 67% identity with ORF5 from V. cholerae. With regard to claim 5, the VCR-2 primer used by Mazel et al. has within it two restriction sites.

Regarding the limitation in step (a) which recites the use of "primers having sequences contained in at least one of SEQ ID NO: 5 through SEQ ID NO: 91" this recitation is extremely broad with regard to the actual structural limitation put on the primer. The use of "having" is equivalent to "comprising," and thus means that the primers must comprise "sequence contained in" at least one of SEQ ID NO: 5 through 91, but can have any number of additional nucleotides on either end of the primers. The length of the "sequence contained in" is entirely undefined, and thus is inclusive of as few as one or two nucleotides. Thus, the primers taught by Mazel et al. share at least one or two nucleotides with the sequences recited in the claim.

Mazel et al. do not teach a step of (c) ligating the DNA fragments of step (b) into a vector for cloning the amplified genes into a host cell, nor do they determine the function of the amplified sequences. Mazel et al. do specifically suggest that due to the large size of the VCR structures, it is likely that the structure functions as a generalized system for the entrapment and spread of biochemical functions (p. 607, 3rd column).

However, at the time the invention was made, it was routine to ligate a DNA fragment into vector prior to sequencing of the fragment. Likewise, it was routine to ligate sequences containing open reading frames into expression vectors for the purpose of further characterizing

the unknown coding sequences. For example, Ogawa et al. teach the isolation of a coding sequence that is flanked by repeats from V. cholerae, cloning of the sequence into a vector (p. 608), and subsequent sequencing of the gene for further characterization. It would have been prima facie obvious at the time the invention was made to have modified the methods taught by Mazel et al. so as to have included a step of cloning the amplified fragments into vectors for sequencing of for expression of the unknown ORF. One would have been motivated to undertake such a transformation in order to have further studied the uncharacterized open reading frame amplified from the V. metschnikovii genomic DNA, as exemplified by Ogowa et al., and also since Mazel et al. specifically suggest that the integrated ORF may contain sequences related to biochemical functions of the cells. Such further analysis would have included determining the sequence and function of the ORF and encoded polypeptide, and necessarily would have included determining "whether" the sequence encodes any type of enzyme, including a methyl transferase or restriction endonuclease. Even if the sequence were determined to encode a polypepetide that is not a methyl transferase or endonuclease, this would have necessarily been a determination that it is not one of these. Therefore, in view of the teachings of Mazel et al. in view of Ogawa et al., the instant invention is prima facie obvious.

Response to Remarks

The remarks are addressed in the order provided in the response, beginning on page 6 of the response.

The rejection of claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Lorenz et al. (Biochemistry and Molecular Biology International, pages 705-713, Vol. 36, No. 4,

July 1995) is WITHDRAWN in view of applicant's amendments to the claim. Lorenz et al. does not teach a step of determining whether the cloned DNA fragments encode at least one of a restriction endonuclease or a methyl transferase. Lorenz et al. do not analyze the cloned sequences to determine the nature of the encoded polypeptides.

The rejection of claims 7 and 11 under 35 U.S.C. 102(b) as being anticipated by Brennan (US 5474796) is WITHDRAWN because Brennan does not teach probing a prokaryotic DNA preparation.

The rejection of claims 7, 11, and 12 under 35 U.S.C. 102(e) as being anticipated by Lansdorp (US 6514693) is WITHDRAWN because Lansdorp does not teach probing a prokaryotic DNA preparation.

The rejection of claims 7, 8, 11, 12, 13, and 14 under 35 U.S.C. 102(b) as being anticipated by Barker et al. (Journal of Bacteriology, Sept 1994; as cited in IDS) is MAINTAINED. Applicant argues that the Barker reference is not directed to methods using an oligonucleotide probe designed to hybridize to the sequences selected from one or more of SEQ ID NO: 5 through SEQ ID NO: 78 under stringent conditions. The specification does not provide a limiting definition of "stringent conditions" and so these are broadly interpreted as including conditions of any stringency- low stringency conditions are stringent, they are simply low stringency. As noted in the rejection, the claim does not define the target sequence which is hybridized (i.e. the claim does not require that the probe actually hybridize to SEQ ID NO: 5), the claim only requires that the probe be "capable" of hybridizing to the sequences under some undisclosed stringent conditions. Thus, the claims remain extremely broad and the rejection is maintained.

A new 102(b) rejection has been set forth to address claim 1 as it has been amended.

The 103 rejection is applied to amended claims 1, 5, and 6. The preamble of the claims as amended recites "a method for cloning at least one of a restriction endonuclease or a methyl transferase," but the process steps of the claims do not require the cloning of such a molecule, only the further characterization of the cloned molecule to determine "whether" it is one of these. The claim does not require, however, the specific assay for one of these activities. Thus, the final process step of the claim is met by a determination of any function of the encoded fragments, since the determination that the encoded polypeptide is, for example, a heat stable toxin would necessarily be a determination that it is not a restriction endonuclease or a methyl transferase. Applicant argues that since Mazel fails to disclose or even suggest that restriction endonuclease and methyl transferase genes could be located within cassette arrays, the disclosure does not address the instant claims. This is not persuasive in view of the rejection as it has been redrafted to suit the amendments to the claims.

Regarding the 112 1st paragraph rejection, applicant argues that the specification need not teach what is well-established in the art, pointing out that Mazel describes how to perform hybridization using oligonucleotides, and how to avoid hairpin formation or primer dimers. This specific discussion is not located in Mazel et al. In the instant case, applicant clearly states in the specification that this is a particularly difficult aspect with regard to the practice of the present invention, but provides no guidance as to how to overcome it commensurate in scope with the instant claims. As noted at the bottom of page 10 of the remarks, specific primers are provided in the specification, and these can be used for the practice of the claimed invention. The instant claims, however, are extremely broad with respect to the probes and primers that can be used,

and encompass the use primers and probes with very little structural similarity to the disclosed SEQ ID NO. This is complicated by the fact that the claims are sufficiently broad in nature to encompass the assay of any organism, or for some claims any prokaryotic organism. However, there is no reason to believe, based on the teachings of the specification nor the prior art, that the instantly disclosed sequences would detect repeat sequences of expression cassettes in organisms other than the Pseudomonas disclosed in the specification. Applicant argues on page 11 of the remarks that "one of ordinary skill would expect similar families of repeats to be present in a wide variety of prokaryotes," however there is no evidence to suggest that these "similar families" can be detected by the sequences disclosed in the instant specification, as discussed in the rejection. The attorney's arguments cannot replace evidence on the record.

Applicant argues that with regard to the determination of the presence or absence of a restriction endonuclease or methyl transferase, that these can be assayed by the assays described in the specification. The issue at hand is not whether or not one could determine if a cloned sequence is in fact one of these enzymes, this is not disputed, it is that it is highly unpredictable whether or not one would even amplify a sequence encoding one of these enzymes using the methods recited in the claims. The rejection discusses the extremely broad nature of the claims regarding the primers to be used as well as the wide variety of species of organisms that could be the target of the methods, etc. Applicant's remarks are not sufficient to overcome the grounds of rejection. The rejection is thus maintained.

Regarding cliams's 7-14, applicant argues that amended claims 7 is enabled for any oligonucleotides that would hybridize under "stringent" conditions, asserting that this term is understood by one of ordinary skill. As discussed previously in this office action, this term is

reasonably broadly interpreted to include conditions of any stringency. Any further limitations that applicant is reading into the claim are not supported by the specification as clearly defining the term. Furthermore, the enablement of the probes themselves is not the sole issue discussed in the rejection, which also discusses the scope of the claims with regard to which species are included in the claims. The rejection is maintained.

Conclusion

11. No claim is allowed.

12. Methods which require oligonucleotides that comprise instant SEQ ID NO: 79 through SEQ ID NO: 91 are free of the prior art as the prior art does not teach or suggest any of these molecules (for example, claim 11).

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached by calling (571) 272-0745.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as

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Juliet C. Switzer
Primary Examiner
Art Unit 1634

September 8, 2005